in the 23Å interaction. Funding: NIH-GM33216, and Welch Foundation A1543.

323-Pos Board B109
Allosteric Control of Cofactor Binding to Nuclear Hormone Receptors
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The nuclear receptor superfamily (NRs) comprises ligand-dependent transcription regulators, many of which function as homodimers or heterodimers with RXR. We show that addition of an SRC-1 coactivator-derived peptide to monomeric liganded retinoic acid receptor (RAR) promotes efficient homodimer formation. X-ray crystallography revealed that homodimers are asymmetrical, reminiscent of functional RXR-RAR heterodimers with distinct conformations of ligand in the two subunits. A global switch to the dimeric state with a 2RAR:1SRC-1 stoichiometry was also seen using a larger 20kDa domain of SRC-1. Our study reveals an allosteric mechanism whereby coactivator binding to one RAR partner affects ligand conformation and H12 position of the second partner, hrough the dimer interface. A similar control on the recruitment of SRC-1 is also observed with ER in the crystal structures of ERa bound to agonist ligands and coactivator peptide.

324-Pos Board B110
Identification of Nuclear Receptor Ligands using Differential Scanning Fluorimetry
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Identification of ligands that interact with nuclear receptors (NRs) is both a major biological problem and an important initial step in drug discovery. Several in vitro and in vivo techniques are commonly used to screen ligand candidates against nuclear receptors, however none of the current assays allow screening without modification of either the protein and/or the ligand in a high-throughput fashion. Differential scanning fluorimetry (DSF) allows unmodified potential ligands to be screened as 10μL reactions in 96-well format against partially purified protein, revealing specific interactors. As a proof of principle, we used a commercially available NR ligand candidate chemical library to identify interactors to several well characterized human NRs. Compounds that interact specifically with NR Ligand Binding Domains stabilize the protein and result in an elevation of the thermal denaturation point as monitored by the environmentally sensitive dye SYPRO orange. We present results validating DSF as a new tool for identifying NR ligands and screening candidate compounds and also present results of orphan NRs currently under investigation.

325-Pos Board B111
The Mode of Action of FtsZ Inhibitors
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Multi-drug-resistant bacterial infection is the primary cause for death in the world. Developing antimicrobial agents that act or inhibit through mechanisms different than those of existing antibacterial drugs offer an advantage in that resistance mutations will not have developed, and thus have a better prospect to efficiently kill bacteria. Over the past decade, a significant advancement has occurred in the use of FtsZ as a target for antimicrobial activity.
FtsZ is a highly conserved multimeric cytoskeleton protein in prokaryotes. It forms a z-ring structure at the middle plane of the bacterial cell, in which cooperation with other bacterial proteins eventually propagates cytokinesis. Binding of GTP to the monomeric FtsZ protein promotes dimerization and protofilament formation. Affecting the GTPase activity of FtsZ will inhibit dimerization/polymerization and subsequent z-ring formation and eventually inhibits bacterial cell division. Therefore, FtsZ has become a promising target for the development of antibacterial drugs.
Recent studies have revealed a number of natural and synthetic small molecules, which target FtsZ and cause lethality in bacteria thus making FtsZ an excellent target for the development of broad-spectrum antimicrobial drugs. These inhibitors are classified on the basis of the mode of action or by origin as natural or synthetic inhibitors. Most inhibitors affect GTPase activity, subsequently affecting cell division. Some inhibitors stabilize protofilaments, which also affects the formation of the z-ring. Whatever mode of action, all these inhibitors are lethal to bacteria. However, the mechanism of how various types of inhibitors binds to FtsZ and eventually inhibits cell division is still to be evaluated. In this study, we will demonstrate, for the first time, how and to what site each inhibitor binds on FtsZ protein. Understanding of this mechanism is crucial for the future development of antimicrobial drugs with high efficacy.

326-Pos Board B112
Charge Discriminates Coreceptor Selectivity for HIV-1
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We have performed physicochemical and statistical analysis of a large dataset of sequences of the V3 loop of the glycoprotein gp120 from HIV-1 strains with known coreceptor selectivity, derived from patient data. The entry of HIV-1 into host cells is mediated by the interaction of the V3 loop of gp120 and coreceptors CCR5 and CXCR4 on host cell surfaces, with the aid of viral protein gp41 and cell receptor CD4. The choice of CCR5 for viral entry is associated with the asymptomatic cell infection, whereas the choice of CXCR4 is associated with progression to disease. Given the sequence and structural variability of the V3 loop, we have searched for persistent physicochemical properties that may be mediators of coreceptor selectivity and binding using the Los Alamos HIV Databases [1]. Our electrostatic analysis demonstrates that charge is the dominant factor that mediates coreceptor selectivity, other factors being the N6XT/SX9 glycosylation motif and the 11/24/25 rule. We have examined amino acid propensities for each position of the V3 loop sequence and identified key amino acids and positions that may affect the coreceptor choice. We have studied the conformational variability of the V3 loop, using molecular dynamics simulations, and identified persistent intramolecular interactions that may be important for maintaining the electrostatic profile of the V3 loop that facilitates coreceptor binding. We have used a statistical model to estimate the probability for coreceptor selectivity, as a function of charge and presence or absence of glycosylation motif and 11/24/25 rule. We present an integrated predictive scheme of coreceptor selectivity and binding, which may be useful in estimating disease progression, and perhaps aiding in tailoring the selection of anti-HIV drugs for individual patients.
[1] http://www.hiv.lanl.gov/content/index.

327-Pos Board B113
Thumbs Down: Subdomain Rearrangements in the Drug Bound HIV-1 Reverse Transcriptase
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One of the two main drug targets in human immunodeficiency virus-1 (HIV-1) therapy is the reverse transcriptase (RT) enzyme. Non-nucleoside RT inhibitors (NNRTIs) are a class of highly specific drugs which bind to a pocket approximately 10 Å from the polymerase active site, inhibiting the enzyme allosterically. It is widely believed that NNRTIs function as ''molecular wedges'', disrupting the region between thumb and palm subdomains of the p66 subunit and locking the thumb in a wide open conformation. Crystal structure data suggests that the binding of NNRTIs forces RT into a wide open conformation in which the separation is between the thumb and fingers subdomains is much higher that the apo structure. Using multi-copy molecular dynamics simulations (with a cumulative simulation time of approximately 900 ns) we have captured RT bound to the NNRTI efavirenz in a previously uncharacterised closed conformation suggesting that the constraint of thumb motion is not as complete as previously believed. This conformation is similar to that adopted by the apo enzyme but with a modified inter-subdomain hinge. We compare the correlated domain motions of the drug bound and apo enzymes. A more detailed understanding of the mechanism of NNRTI inhibition and the effect of their binding upon domain motion could aid the design of more effective inhibitors and help identify novel allosteric sights.

328-Pos Board B114
Understanding Chlorocatechol 1,2-Dioxygenase Function: A Promising Player in Bioremediation Processes
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Dioxygenases are bacterial nonheme iron enzymes responsible for the aerobic catabolism of several intermediates produced by the decomposition of aromatic compounds that are industrially released in the environment and recalcitrant to